Remarks

The Examiner Interview

On August 29, 2007, the undersigned met with Examiner Valenrod and Primary Examiner Barts at the United States Patent and Trademark Office. An Interview Summary under 37 C.F.R. 1.133(b) was filed by Applicants in the present application on September 18, 2007. The undersigned thanks Examiners Valenrod and Barts again for the opportunity to meet with them, and for the courteous and frank discussion.

Rejection Under 35 U.S.C. § 103

In the Office Action mailed May 23, 2007, the Examiner rejected claims 1-18, 21, 22, 23, 26-28 and 30-36 under 35 U.S.C. § 103(a) as allegedly being obvious over Rewinkel *et al.*, *Curr. Pharm. Design* 5:1043-1075 (1999) (hereinafter "Rewinkel"), in view of de Nanteuil *et al.*, U.S. Patent No. 5,814,622 (hereinafter "de Nanteuil") and in further view of Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams").

Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established. Even if, *inter alia*, a *prima facie* case of obviousness had been established, it is rebutted by the surprising results provided by the claimed invention.

Briefly, the Examiner asserts (1) that Rewinkel discloses a boronic acid having a methoxyalkyl substituent for R9 in present claim 1, a proline as recited in claim 17, a hydrophobic moiety in the form of a diphenylalanine residue, and a protected N-terminal amine group, along with a Ki for thrombin inhibition of 14 nM which is below 100 nM as recited in present claims 7 and 28; (2) that de Nanteuil discloses organoboronic acids

and pharmaceutically acceptable salts thereof; and (3) that Adams discloses that pharmaceutically acceptable salts of organoboronic acids include alkaline metal salts, alkaline earth metal salts, and amino salts. Therefore, according to the Examiner, it would have been *prima facie* obvious for one of ordinary skill to have taken the organoboronic acid compounds of Rewinkel, and modify them in view of the disclosure of Adams by creating pharmaceutically acceptable salts thereof to produce the presently claimed compounds and compositions. Applicants respectfully disagree with these conclusions and the reasoning upon which they are based.

Applicants reiterate their arguments already of record, subject to certain clarifications provided herein. Moreover, Applicants provide the following additional arguments, based on the evidence filed herewith in the form of the Kennedy Declaration.

The present invention provides pharmaceutically acceptable base addition salts of peptidyl boronic acids having the chemical structure recited in the claims. These peptidyl boronic acid base addition salts are useful as thrombin inhibitors. In order for a compound to be pharmaceutically useful as a thrombin inhibitor, it must have sufficient stability for an acceptable shelf life. Kennedy Declaration at ¶ 5. As Dr. Kennedy explains, the art, *i.e.*, Wu *et al.*, *J. Pharm. Sci. 89*: 758 (2000) (hereinafter "Wu"), which is of record in the present application, points away from converting a peptidyl boronic acid to its boronate salt, because Wu states that *inter alia* alkaline conditions should not be favorable to stability. Kennedy Declaration at ¶ 21. However, salt manufacture involves exposing an acid to a base. Moreover, as discussed in the remainder of the Kennedy Declaration, the cited art provides no reason for one of ordinary skill in the art

to conclude that base addition salts of peptidyl boronic acids would be more stable than the corresponding free acid.

Unlike ordinary peptides, peptidyl boronic acids are not carboxylic acids. Whereas an ordinary peptide contains a carboxyl group, a peptidyl boronic acid contains a boryonyl group. Kennedy Declaration at ¶ 7. As Dr. Kennedy explains, peptidyl boronic acid chemistry presented him with unique difficulties, because boron does not behave like carbon and presents some unusual challenges in pharmaceutical development. *Id.*

Compared to carboxylic acids, which are relatively stable, peptidyl boronic acids exhibit an inherent degradative instability of the boronyl group. Kennedy Declaration at ¶ 8. Owing to the $-B(OH)_2$ structure of peptidyl boronic acids, the peptidyl boronic acids can form diol stable esters, which carboxylic acids cannot form. *Id.* One example of such a boronic diol ester is the marketed formulation of peptidyl boronic acid N-(2-pyrazine) carbonyl-L-phenylalanine-L-leucine boronate, whose International Nonproprietary Name is bortezomib (previously known as MG-341). Bortezomib as sold comprises the mannitol ester of the peptidyl boronic acid. Kennedy Declaration at ¶ 24. This peptidyl boronic acid is described in Adams, in Wu and in Gupta *et al.*, WO 02/059130 (hereinafter "Gupta"), which is of record in the present application. Wu and Gupta describe the instability of bortezomib, *id.* at ¶¶ 21-23, while Gupta points to esterification with a diol, in particular the lyophilized D-mannitol ester, as the route to stability. *Id.* at ¶ 23. Thus, remarkable changes in chemistry are afforded by replacing a carboxy group (-COOH) with a boronyl group $-B(OH)_2$. *Id.*

Given the physicochemical differences between carbon and boron, discussed by Dr. Kennedy in ¶¶ 7 and 8 of his declaration, one of ordinary skill in the art would have been extremely cautious in extrapolating the physicochemical behavior of a carboxylic acid drug to draw any conclusions regarding the physicochemical behavior of a boronic acid drug. Kennedy Declaration at ¶ 9. Thus, as discussed below, the Examiner's reliance on Davies *et al.*, *The Pharmaceutical Journal 266*: 322 (2001) (hereinafter "Davies") at page 4 of the Office Action is misplaced. Moreover, as discussed below, a comparison between the Applicants' data and Davies shows that the disclosure of Davies that stability can be decreased by converting a compound to a salt of increased solubility does not work with peptidyl boronic acids. It is therefore inappropriate for Davies to be applied to such compounds.

Within the class of compounds encompassed by the claimed invention is a base addition salt of a compound called TRI 50c, which is being developed by the assignee of the present application, Trigen Limited, as a candidate active pharmaceutical ingredient ("API"). Kennedy Declaration at ¶ 10. TRI 50c is a second generation candidate API. *Id.* The first generation API was a pinacol ester of TRI 50c that was known as TRI 50b. *Id.* TRI 50c is the free acid of TRI 50b. Specification at page 9, line 28. TRI 50c has never been sold as a drug in any form. Kennedy Declaration at ¶ 11

Rewinkel is a review article and one of the thrombin inhibitors it describes on page 1052 is Compound 21. Kennedy Declaration at ¶ 13. However, Rewinkel fails to show the correct structure of Compound 21. *Id.* In order to understand what Rewinkel discloses, one must consult the reference to which Rewinkel refers. *Id.* At page 1054, second paragraph, referring to Compound 21, Rewinkel cites Deadman *et al.*, *J. Med.*

Chem. 38: 1511 (1995) (hereinafter "Deadman"). Kennedy Declaration at ¶ 13. Deadman is of record in the present application. Rewinkel's Compound 21 is a pinanediol ester. Kennedy Declaration at ¶14.

Dr. Kennedy also explains that, although De Nanteuil and Adams disclose certain boronic acids and certain salts that purportedly can be made, the only salts that De Nanteuil and Adams actually made were acid addition salts, not base addition salts. Kennedy Declaration at ¶ 16.

Peptidyl boronic acid salts are unstable and TRI 50c has significant stability problems, which make the molecule extremely difficult or impossible to put into a pharmaceutical formulation with adequate stability, *i.e.*, shelf life, for practical use. Kennedy Declaration at ¶ 17. The claimed invention is thus directed to making pharmaceutical formulations. *Id.* The challenge for the inventors in the present application was to identify derivatives of peptidyl boronates which would be stable enough for pharmaceutical use. Kennedy Declaration at ¶ 18.

As Dr. Kennedy understands the Examiner's position, it would have been allegedly obvious to make base addition salts of any of the peptidyl boronic acids of Adams, in order to enhance their stability, since it was supposedly obvious to try base addition salts. Kennedy Declaration at ¶ 19. One of the compounds discussed in Adams is N-(2-pyrazine)carbonyl-L-pheynylalamine-L-leucine boronic acid, which is MG-341. *Id.* In Adams, pharmaceutical salts and esters are said to be "preferred." *Id.* Dr. Kennedy reiterates, however, that the chemical behavior of boron is unique, and there was in his opinion no basis for supposing that base addition salts would be preferred.

Kennedy Declaration at ¶ 20. Indeed, later work on MG-341 related to a stable formulation as a mannitol ester, which points away from making a base addition salt. *Id.*

Moreover, Wu discusses MG-341 and teaches away from making a base addition salt. Citing Wu at page 758, Dr. Kennedy explains that Wu states:

> *The chemical stability of peptide boronic acid derivatives, from a formulation perspective, has not been extensively reported in the literature to our knowledge. During an effort to formulate 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ for parenteral administration, the compound showed erratic stability behaviour and was quite unstable in certain solvents.*

Kennedy Declaration at ¶ 21.

Citing Wu at page 763, Dr. Kennedy explains that Wu states:

> *Based on the known chemistry of boronic acids and the identity of the degradants, a degradation pathway of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ was proposed and is illustrated in Scheme 1. The initial oxidation can be attributed to peroxides or molecular oxygen and its radicals.* ***Because light, metal ions and alkaline conditions normally facilitate oxidation these conditions should not be favorable to the stability of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ or any other alkyl boronic acid derivative****. Consistent with this conclusion is the observation that light accelerated the degradation of 2-Pyz-(CO)-Phe-Leu B(OH)$_2$.* (Emphasis added).

Kennedy Declaration at ¶ 21.

Turning to Gupta, Dr. Kennedy explains that, while Gupta relates to a class of boronic acids, all the examples in Gupta describe 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$, *i.e.*, MG-341. Kennedy Declaration at ¶ 22. Gupta also acknowledges that boronic acids are unstable, as evidenced by their oxidization by air. *Id.* Gupta also discloses that, whereas the lyophilized D-mannitol ester of MG-341 was stable over a period of 18 months, the free acid was not stable for longer than 6 months. Kennedy Declaration at ¶ 23.

Dr. Kennedy further explains that MG-341, *i.e.*, bortezomib, is now sold under the trade name Velcade.® Kennedy Declaration at ¶ 24. A copy of the Velcade® package insert is attached to the Kennedy Declaration. As Dr. Kennedy explains, bortezomib is sold as a lyophilized powder of the mannitol ester of the free boronic acid. Kennedy Declaration at ¶ 24.

Elaborating on the chemistry of boronic acids, Dr. Kennedy explains that boric acid ($B(OH)_3$) is a weak acid. Kennedy Declaration at ¶ 25. The present application claims priority benefit of applications filed in Great Britain in September, 2002. In Dr. Kennedy's opinion, in September, 2002, the chemist of ordinary skill in the art would have concluded that peptidyl boronic acids are weak acids, and that the salts of weak acids with strong bases form basic solutions. *Id.* Dr. Kennedy concludes that it would have been reasonable to predict that salts of peptidyl boronic acids with a strong base, such as sodium hydroxide, would form basic solutions. *Id.* According to Wu, however, a basic solution would adversely affect stability. *Id.*

Dr. Kennedy explains that in September, 2002, one of ordinary skill in the art would have concluded that:

(1) peptidyl boronic acids are prone to oxidative degradation and, because light, metal ions and alkaline conditions normally facilitate oxidation, these conditions should not be favorable to stability;

(2) peptidyl boronic acids are weak acids and will form alkaline solutions with strong bases;

(3) base addition salts of peptidyl boronic acids had never been tested for their stability for formulating;

(4) but their esters had been tested (citing Gupta and the assignee's work on TRI 50b);

(5) bortezomib was excessively unstable (citing Gupta and Wu); and

(6) bortezomib was stabilized by manufacture as an ester, namely its lyophilized D-mannitol ester.

Kennedy Declaration at ¶ 26.

Accordingly, Wu would have pointed one of ordinary skill in the art away from using alkaline conditions, and Gupta would have pointed him toward making an ester, in order to increase stability. Kennedy Declaration at ¶¶ 26 and 27. Indeed, anyone reading Wu's disclosure that alkaline conditions destabilize peptidyl boronic acids, would have been surprised to learn that a peptidyl boronic acid could be stabilized by combining the acid with alkali, to form a salt. *Id.* The destabilizing effect of alkaline conditions is specific to boronic acid chemistry, which is very different from the more mainstream carboxylic acid chemistry. Kennedy Declaration at ¶ 28.

Referring to Davies, Dr. Kennedy explains that Davies relates to the selection of salts from an available "pool" of salts. Kennedy Declaration at ¶ 29. However, for peptidyl boronic acids, there was not an available pool of base addition salts. *Id.* Thus, Davies fails to provide a starting point for further consideration, so far as base addition salts of peptidyl boronic acids are concerned. *Id.* Unlike Davies, which is concerned with the selection of salts in a context where changing a drug from its free base or acid to a salt form is commonly done to improve its kinetics, absorption or physicochemical properties, here, changing a boronic acid drug from its free acid to a salt form to improve its kinetics, absorption or physicochemical properties is not commonly done, and so far

as Dr. Kennedy is aware, has never previously been done. *Id.* Davies is not informative, because, to Dr. Kennedy's knowledge, the effects on such properties of converting a peptidyl boronic acid to a base addition salt had never been researched. *Id.* Indeed, to Dr. Kennedy's knowledge, there had never been any suggestion that the chemistry of peptidyl boronic acids made such acids suitable to pharmaceutical formulation as base addition salts. *Id.*

In Dr. Kennedy's view, the ordinarily skilled worker would have had no reasonable expectation that base addition salts of the claimed peptidyl boronic acids would exhibit enhanced stability. Kennedy Declaration at ¶ 31. Adams and de Nanteuil do not recognize the challenges associated with shelf life and its associated requirement for adequate stability. *Id.* Moreover, the researchers who developed bortezomib decided to stabilize it by derivatization as a mannitol ester. *Id.* Finally, one of ordinary skill in the art would have been led by Wu away from base addition salts. *Id.*

Against Wu's teaching that peptidyl boronic acid salts would be unstable, the present invention couterintuitively achieves stability for the claimed class of peptidyl boronic acids by formulating them as boronate salts. Kennedy Declaration at ¶ 32. Dr. Kennedy discusses the data previously presented in the present application. Thus, the Summary Stability Report, filed with the Amendment and Reply filed March 20, 2007, shows in Table 1 that the free acid TRI 50c degraded dramatically over three months at 25°C, and shows in Table 2 that the purity of the free acid decreases from 97.18% to 58.83% over three months at 25°C. *Id.* In contrast to the TRI 50c free acid, the purity of the TRI 50c sodium salt decreased only to 95.3% when stored for three months at 25°C. *Id.*

The data in the stability report are consistent with the stability data provided in Examples 27 and 28 of the present application, in which the sodium and lysine salts were shown to be more stable than the free acid. Kennedy Declaration ¶ 33. The data in the stability report are also consistent with the data reported in Example 13 of U.S. Patent No. 7,112,572, which shows that the calcium salt of TRI 50c is more stable than the free acid. Kennedy Declaration at ¶ 33. Dr. Kennedy summarizes the stability data in ¶ 34 of his declaration, and explains that not only are the TRI 50c salts listed in the table in ¶ 34 stable, they are also soluble.

Finally, Dr. Kennedy reiterates that articles such as Davies and Berge *et al.*, *J. Pharm. Sci. 66*: 1 (1977) (hereinafter "Berge") are not relevant to the presently claimed invention. Kennedy Declaration at ¶ 35. For example, the "Stability" section of Davies, on page 323, describes that highly polar salts create a surface favoring wettability and that this can *reduce* stability. Kennedy Declaration at ¶ 35 (emphasis added). Davies further discloses that the formation of salts with low water solubility is a means of increasing the chemical stability of a drug that is susceptible to heat and moisture. *Id.*

Turning to Berge, which is of record in the present application, Dr. Kennedy explains that in the paragraph in Berge bridging the columns on page 9, sparingly soluble salts reduce the amount of drug in solution and hence reduce degradation. Kennedy Declaration at ¶ 35. Berge also states that the acceptable stability of the salts of penicillin G in aqueous solution is based mainly on their insolubility and the minimization of degradation in solution. *Id.* Thus, whereas Davies and Berge provide that the stability of an unstable acid could be improved by converting the acid into a salt of *reduced* solubility, the data presented in ¶ 34 show that derivatization of TRI 50c as a

range of base addition salts increases stability, and the sodium salt of TRI 50c, which is about ten times more soluble than TRI 50c, is significantly more stable than the free acid. Kennedy Declaration at ¶ 35.

Dr. Kennedy concludes by stating again that Wu points away from combining boronic acid drugs with a base, because alkaline conditions are described as promoting instability, and Gupta points toward stabilizing boronic acid drugs as D-mannitol esters. Kennedy Declaration at ¶ 36. As a result, one of ordinary skill in the art would have found it surprising that the claimed base addition salts of peptidyl boronic acids would have been more stable than the free acids.

As the Federal Circuit recently explained in *In re Sullivan*, 2007 U.S. App. LEXIS 20600, *12-13 (Fed. Cir. 2007), the Office is obligated to consider rebuttal evidence when evaluating the nonobviousness of a claimed invention. Evidence in the form of a declaration, such as the Kennedy Declaration filed herewith, is rebuttal evidence. *Id.* at *14-16.

In *Sullivan*, the Board of Patent Appeals and Interferences failed to consider rebuttal evidence in the form a declaration by an expert and two declarations by two of the co-inventors of the appealed application. *Id.* at *14-16. The Federal Circuit explained that the Office must give meaningful consideration to rebuttal evidence, including evidence of how the prior art teaches away from the claimed invention. *Id.* at *17-18.

Here, rebuttal evidence has been provided in the form of the Kennedy Declaration, which shows that Wu and Gupta teach away from the claimed base addition

salts of peptidyl boronic acids, such that the claimed invention would have been surprising.

Applicants respectfully request that the obviousness rejection be reconsidered and withdrawn.

Applicants also wish to clarify certain remarks made in previous replies. In the Amendment and Reply filed August 17, 2007, at page 22, line 6, Applicants referred to Wu and Gupta in the context of stabilization of the active ingredient in Velcade® as an ester. The reference to Wu in that context was incorrect.

In the same Amendment and Reply, at page 23, first full sentence, Applicants referred to previous solutions to stabilizing boronic acids as including lyophilization or esterification. Applicants were referring to their earlier discussion of Gupta in the same document at page 21. Applicants wish to clarify that, as discussed herein, Gupta refers to a lyophilized ester, not to lyophilization as such. Gupta describes esters, and more particularly sugar esters, while Gupta's examples, and therefore data, relate to lyophilized D-mannitol ester of 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$, the stability of which was found to compare favorably with the acid (see Example 5 of Gupta).

Applicants also wish to revisit their discussion of Martichinok, *J. Am. Chem. Soc. 118*: 950-58 (1996) (hereinafter "Martichonok"). At page 22 of the Amendment and Reply filed on March 20, 2007, Applicants discussed that in Martichinok at page 951, right-hand column, the authors made a diethanolamine ester to impart stability to boronic acids. At page 21 of the Amendment and Reply filed August 17, 2007, in footnote 1, Applicants explained that Martichonok referred to diethanolamine derivatives, not to an ester. However, in referring again to Martichnok, Applicants realize that at page 951,

right-hand column, Martichonok refers to "diethanolamine derivatives **6** by reaction with diethanolamine in 2-propanol." Referring to "Scheme 1" at the top of page 951 of Martichonok, one sees that the "diethanolamine derivative **6**" is a diol ester formed from the reaction of the boronic acid with diethanolamine.

Amendment and Reply filed on March, 2007, Applicants referred to Matteson *et al.*, U.S. Patent No. 5,681,978 (hereinafter "the Matteson '978 patent") in the paragraph bridging pages 22 and 23, pointed to column 4, lines 57-67, and stated that the Matteson '978 patent relates to oxidative resistance of a pinacol ester of a boronic acid. Upon subsequent review, Applicants now realize that this statement was in error, since Matteson refers to oxidative resistance of a diol, not to an ester. Accordingly, Applicants respectfully wish to correct the record, with respect to the disclosure of the Matteson '978 patent. Moreover, by the foregoing amendment, the incorrect description of the Matteson '978 patent has been deleted from the present Specification.

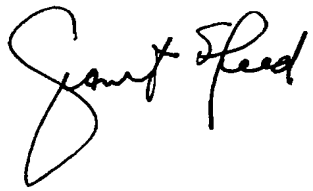
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this supplemental Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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